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Intestinal failure associated cholestasis in surgical necrotizing enterocolitis and spontaneous intestinal perforation

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ABSTRACT

Background: Surgery for necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) is often complicated by intestinal failure (IF) and intestinal failure associated cholestasis (IFAC).

Objective: Assessment of incidence, predictors, and mortality associated with IFAC in surgically treated NEC and SIP.

Methods: A retrospective observational study based on hospital records during 1986–2014 in the two largest Finnish neonatal intensive care units was performed. IFAC was defined as conjugated bilirubin >34 $\mu\text{mol/l}$ (2.0 mg/dl) for \geq two postoperative weeks while receiving parenteral nutrition (PN).

Results: In total 225 patients underwent surgery for NEC ($n = 142$; 63%) or SIP ($n = 83$; 37%). Included were 57 survivors with \geq two weeks PN. Sixty-five (42%) patients developed IFAC. Two-year survival with IFAC was 80% and without IFAC 89% ($p = 0.13$). Of the 65 patients with IFAC, all eight with unresolved IFAC died in comparison to six of 57 (11%) whose IFAC resolved ($p < 0.0001$), while IFAC resolved in all survivors. Survival among patients with resolved IFAC was 89% and with unresolved IFAC ($n = 8$) 0%, ($p < 0.0001$). IFAC lasted for median 83 (IQR 45–120) days and correlated with the duration of PN ($R^2 = 0.16$, $p = 0.03$), delay of starting enteral feeds ($R^2 = 0.12$, $p = 0.05$) and PN lipid emulsion ($RR = 1.0$ (95% CI = 1.0–1.1) ($p = 0.02$). In multivariate logistic regression analysis, IFAC development associated with septicemias and reoperations.

Conclusions: 42% of prematures who underwent surgery for NEC or SIP developed IFAC. Reoperations and septicemias increased the risk of IFAC. None of the patients with unresolved IFAC survived, but IFAC did not increase overall mortality.

Type of study: Retrospective prognosis study.

Level of evidence: Level II.

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Cholestasis is a common and severe complication in neonates who undergo extensive intestinal surgery and receive parenteral nutrition for long periods of time. Necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP) are the most common intestinal diseases of premature infants. NEC or SIP occurs in as much as 2% of patients in neonatal intensive care units (NICU) [1–4]. In patients with Bell stage III NEC [5] or SIP, surgery is almost invariably required. Mortality in surgically treated NEC remains high ranging from 30% to 50% [6–8]. Because of extensive loss of small intestine and impaired motility of remaining intestine, surgery for NEC or SIP is accompanied with intestinal failure (IF) in as many as 42% of patients [9,10], and long periods of parenteral nutrition (PN) are required. In pediatric IF development of cholestasis is a poor prognostic sign [11]. Even if intestinal failure

associated cholestasis (IFAC) resolves, significant liver fibrosis and steatosis may persist years after surgery and weaning off PN [12].

In this retrospective observational study we assessed IFAC in patients with surgically treated NEC or SIP in two major level III NICUs in Finland. During the study period from 1986 to 2014 there were a total of 22,000 admissions in both NICUs. Main outcome measures were incidence of IFAC, risk factors of IFAC development and effect of IFAC on mortality.

1. Methods

The Ethical Review Board approved this study. Data including operative details, duration of PN and septicemias with positive blood culture, were collected from the hospital records. Included were premature (gestation age < 37 weeks) neonates who underwent surgery owing to acute deterioration caused by NEC (radiological signs consistent with of Bell stage III) or SIP. NEC and SIP were differentiated according to 1) preoperative diagnostics: SIP was characterized by intestinal perforation with free gas in plain x-ray, NEC occurred with or without

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perforation with clinical signs of Bell stage II or III 2) findings during the surgery: in SIP there was a single perforation without or with a limited (≤ 2 cm) length of ischemic intestine, in NEC there was a significant segment of ischemic intestine with or without perforation and sometimes several affected sites of intestine could be observed 3) supportive data from pathologist's report of the resected intestine.

Patients with intestinal conditions inconsistent with NEC of SIP, stricture after conservatively managed NEC, NEC related intestinal necrosis in term or almost term (> 37 weeks) babies with cardiac disease or gastroschisis, were excluded.

In both centers (NICUA and NICUB) pediatric surgical services were located in the same hospital building enabling prompt consultations and surgeries were performed in NICU. Soybean oil based PN lipid emulsion (Intralipid®) was used in NICUA from 1986 to 1995 and in NICUB from 1986 to 2007. NICUA used PN lipid emulsion containing 50:50 soy-bean oil and medium-chain triglyceride emulsions (Vasolipid®) from 1996 to 2001. PN lipid emulsion containing 80% of olive oil and 20% soy-oil (Clinoleic®) was used in NICUA from 2001 on and in NICUB from 2008 on. During the last years of the study period PN lipid emulsion containing soybean oil, olive oil rich medium-chain triglycerides and fish oil (SMOF) was used in a small number of patients. For reasons of simplicity comparisons concerning PN lipid emulsions were performed between emulsions based on soy-bean oil (Intralipid®) and other PN emulsions (Vasolipid® and Clinoleic®, SMOF).

IFAC was defined by conjugated bilirubin $> 34 \mu\text{mol/l}$ (2.0 mg/dl) for ≥ 2 postoperative weeks while receiving PN only or PN with enteral nutrition. Bilirubin was measured on clinical indications including jaundice on PN and estimated duration of PN and IF exceeding one week. Measurements occurred at least once a week when bilirubin values were rising, or once in two weeks when the values remained high or began to sink.

Patients who died within two weeks after the first surgery or had PN less than 14 days, were excluded from the final assessment. Survival after

surgery was assessed up to two years. Predictive factors for the development of IF-associated cholestasis were tested with univariate Logistic Regression. Test included birth weight (BW) and gestation age (GA), treating center (NICUA, NICUB), gender, respiratory distress syndrome (RDS), Apgar points, heart disease and patent ductus arteriosus, age at first surgery, diagnosis (NEC vs SIP), relative loss (%) of gestation age-adjusted length of the small intestine [13], type of operation (enterostomy vs primary anastomosis), loss of ileocecal valve, any intestinal reoperations excluding final closure of enterostomies, length of PN, start of PN and enteral nutrition (EN) in relation to surgery, total number of septicemias (= clinical septicemia with positive blood culture) during PN, early (1986–2000) vs late (2001–14) study period and soy-bean based vs other PN lipid emulsion. Because the incidence of IFAC may depend on the relative number of patients who survived two weeks after surgery, we compared 2 week survival in early (1986–2000) (116 patients) and late (2001–2014) (109 patients) periods of the study as well as periods with PN A (109 patients) and PN B (116 patients).

Statistical calculations were made with StatView 512 computer program (Brain Power, Calabasas, CA). If not otherwise stated data are presented as medians with IQR (= interquartile range) or frequencies. Continuous variables were compared with Mann–Whitney and Kruskal–Wallis tests, nominal values with Fischer's Exact Test. Cumulative survival was analyzed with Kaplan–Meier analysis. Predictors for IFAC and for resolution of IFAC were analyzed with Cox proportional hazard regression analysis, generating risk ratios with 95% confidence interval. Numerical correlations with Simple Regression Test Statistically significant independent predictors were included in the multivariate model; p-values below .05 were considered significant.

2. Results

In total 225 patients from 1986 to 2014 with NEC or SIP, 131 (58%) from NICUA and 94 (42%) from NICUB, were assessed. Sixty-eight

Table 1

Clinical data of 157 patients who were assessed for IFAC (Of the total number of 225 patients 68 either with PN duration < 14 days ($n = 21$) or death < 14 days after surgery were excluded).

	No IFAC ($n = 92$)	IFAC ($n = 65$)	
NICU			
A (100)	61 (61%)	39 (39%)	0.5
B (57)	31 (54%)	26 (46%)	
Era			
1986–2000 (79)	53 (68%)	26 (32%)	0.03
2001–2014 (78)	39 (50%)	39 (50%)	
NEC vs SIP			
NEC ($n = 98$)	51 (52%)	47 (48%)	0.04
SIP ($n = 59$)	41 (69%)	18 (31%)	
Birth weight, g	968 (760–1145)	760 (651–1056)*	0.004
Gestation age, weeks	27 (25–29)	26 (25–28)	0.19
Age at first surgery, days	9(6–15)	10 (7–20)	0.23
Apgar score			
1 min	5 (3–6)	5 (3–6)	0.84
10 min	7 (5–8)	7 (5–8)	0.56
Mechanical ventilation, weeks	3.0(1.0–5.0)	5.0(2.0–7.1)*	0.01
Cerebral hemorrhage			
Grade I–II	16 (18%)	14 (22%)	0.54
Grade III–IV	24 (26%)	11 (17%)	0.24
Severe / moderate RDS	46(50%)	33 (51%)	0.94
PDA, no therapy	43 (47%)	36 (55%)	
PDA, medical or surgical therapy	49 (53%)	29 (45%)	0.33
Other significant heart disease	10 (11%)	6 (9%)	0.11
Resection of small intestine %	10 (3–22)	20 (7–49)	0.001
PN lipid solution			
soy oil based ($n = 67$)	43 (64%)	24 (36%)	
other ($n = 90$)	49 (54%)	41(64%)	0.25
Length of PN days	32(21–49)	70(36–150)	< 0.0001
PN before surgery, days	2(0–7)	1(0–3)	0.03
EN started after surgery, days	7(4–14)	15(8–36)	< 0.0001
Number of septicemias	1(0–1)	1(1–2)	< 0.0001
Survival			
3 months	85 (92%)	59 (91%)	0.77
2 years	84 (89%)	52 (80%)	0.06

Table 2

Location of disease, loss of gestation age adjusted intestinal length (%), surgical management and reoperations in 157 patients with NEC or SIP.

	No IFAC (n = 92)	IFAC (n = 65)	
Primary location of disease			
Small intestine	80(92%)	60(87%)	0.43
Colon	12 (8%)	5 (13%)	
Resection of small intestine (%) (n = 140)	10 (3.2–24)	21 (8–51)	0.001
Resection of colon (%) (n = 17)	6.0 (3.0–12)	5.0 (4.2–5.0)	0.45
Type of first surgery			
-resection and enterostomy	64 (70%)	45 (69%)	
-resection and primary anastomosis	28 (30%)	16 (25%)	
-drainage	0	4 (6%) ^a	0.20
Ileocecal valve resected (n = 35)	13(14%)	22 (63%)	0.006
Reoperations (patients reoperated) ^b	25 (27%)	43 (66%)	<0.001
Reoperations (surgeries /patient) ^b	0 (0–1)	1(0–2)	<0.001
Final technique after reoperations			
-enterostomy (n = 123)	69 (75%)	54 (83%)	0.25
-primary anastomosis (n = 34)	23 (25%)	11 (17%)	

^a All patients with drain as primary surgery underwent a reoperation, i.e., enterostomy.

^b Final enterostomy closure excluded.

patients who either did not survive for 2 weeks after surgery (n = 47) or had PN for less than 14 days (n = 21) were excluded. Two week survival in the period 1986–2000 was 76% and in 2001–2014 was 84% (p = 0.15). The final assessment of IFAC included 157 (70%) of 225 patients.

IFAC developed in 65 (41%) of 157 patients. Of 34 patients who remained with PN three months after surgery 26 (76%) developed IFAC. IFAC manifested a median of 18(7–42) days after surgery. Before resolution median duration of IFAC was 83(45–120) days. Independent factors that correlated with the length of IFAC were the length of PN ($R^2 = 0.16$, $p = 0.03$), time to starting enteral feeds after surgery ($R^2 = 0.12$, $p = 0.05$) and use of other PN lipid emulsion (RR = 1.04, 95% CI = 1.01–1.07) ($p = 0.02$).

The incidence of the IFAC increased from 32% during the early study period (1986–2000) (79 patients) to 50% during the late period (2001–14) (78 patients) ($p = 0.04$). Clinical data of patients who developed and did not develop IFAC are outlined in Table 1. Statistically significant differences between patients who did or did not develop IFAC included the intestinal disease (NEC), birth weight, time in mechanical ventilation, loss of small intestine, length of PN (= from start of PN to total weaning), start of PN before surgery, start of enteral nutrition after surgery and number of septicemias.

Surgical procedures are outlined in Table 2. Surgical techniques were similar in patients who developed or did not develop IFAC. Excluding the final enterostomy closures, reoperations were performed to a total of 78 (50%) patients. Of the 124 patients with enterostomy, 114 (75%) survived to undergo final enterostomy closure, which occurred after a median of 9.5 (5.7–14) weeks after the first surgery.

Table 3

Predictive factors for the development of IFAC in logistic regression analysis.

	Univariate analysis		Multivariate analysis	
	RR (95% CI)	p	RR (95% CI)	p
Era (2001–2014)	2.0 (1.1–3.9)	0.03		0.37
Birth weight	0.999 (0.998–1.0)	0.03		0.33
% of small intestine resected	1.024 (1.009–1.04)	0.002		0.55
Septicemias (number of)	1.8 (1.3–2.6)	0.001	1.6 (1.0–2.3)	0.05
Reoperations (number of surgeries)	5.5 (2.8–11)	<0.001	2.1 (1.2–3.6)	0.006
NEC (vs SIP)	2.1 (1.1–4.1)	0.03		0.88
Ileocecal valve resected	3.1(1.4–6.7)	0.004		0.61
Duration of PN (PN)	1.007 (1.002–1.012)	0.03		0.51
Start of PN at or after surgery	2.0 (1.0–3.9)	0.04		0.07
Time to start of EN after surgery	1.012 (1.0–1.024)	0.04		0.82

Factors that in Logistic Regression Analysis predisposed to IFAC are outlined in Table 3. The strongest predisposing factors were number of septicemias and number of reoperations (Table 3).

Two-year survival among the 157 patients was 85 (95% CI = 80–91) %. From the early (1986–2000) to the late (2001–14) era survival improved from 80 (95% CI = 71–89) % to 91 (95% CI = 85–97) % ($p = 0.04$).

Ten (11%) of 92 patients without IFAC and fourteen (22%) of 65 patients with IFAC died ($p = 0.07$); the median age at death was 41 (28–140) days and 140 (48–221) days, respectively ($p = 0.04$). Effect of IFAC on 3-month and 2-year survival was not statistically significant. Three-month cumulative survival in patients without IFAC (n = 92) was 92 (95% CI = 84–96%) % and with IFAC (n = 65) 91 (95% CI = 84–98%) %, and two-year survival was 89 (95% CI = 83–96) % and 80 (95% CI = 70–90) % respectively, Log-Rank Mantel–Cox, $p = 0.13$. Survival with IFAC during early era (1986–2000) (73; 95% CI = 56–90%) and during late era (2001–14) (85; 95% CI = 73–96%) was comparable ($p = 0.28$).

2.1. Resolution of IFAC

IFAC resolved in 57 and did not resolve in eight patients. Comparison of clinical data between patients with resolved and unresolved IFAC is shown in Table 4. Predisposing factors for nonresolution of IFAC were assessed with Logistic Regression Analysis, but none were found. Of eight patients with unresolved IFAC none survived 2 years. Causes of death were recurrent multiorgan failure (n = 4), septicemia (n = 2) and liver failure (n = 2). In two patients multiorgan failure was triggered by recurrent intestinal disease. Laboratory tests including serum conjugated and unconjugated bilirubin, bile acids, gamma-glutamyl transferase and transaminases of the eight patients with unresolved IFAC showed no signs of beginning resolution of IFAC. None of patients with unresolved IFAC were suitable candidates for liver transplantation.

2.2. Parenteral nutrition

Overall median duration of PN was 42(24–74) days. At one month 53/150 (35%) and at three months 110/144 (76%) of the survivors were weaned from PN. Median duration of PN in patients with IFAC was 70 (36–150) days and significantly longer than 32 (21–49) days in patients without IFAC ($p < 0.001$). Of 134 patients who survived two years (IFAC n = 52, no IFAC n = 82), 133 were weaned from PN. Of 23 patients who did not survive two years five died weaned from PN and 18 on PN at the median age of 182 (151–550) and 48 (36–140) days, respectively ($p = 0.02$). Among patients in whom duration of PN exceeded 90 days (n = 33), two-year survival in patients with soy oil based PN (n = 11) was 46% (95% CI = 16–75) compared with 91% (95% CI = 79–102) in patients with other lipid emulsions (n = 22), Log Rank Mantel Cox, $p = 0.0045$. Enteral nutrition (EN) could be started median 9 (5–21) days after surgery. Start of EN in

Table 4

Comparison of clinical data between patients with resolved and nonresolved IFAC.

		IFAC resolved	IFAC not resolved	
		57	8	
NICU				
A (n = 39)		35/39 (90%)	4/39 (10%)	0.70
B (n = 26)		22/26 (85%)	4/26 (15%)	
Era				
1986–2000 (n = 26)		22/26 (85%)	4/26 (15%)	0.70
2001–2014 (n = 39)		35/39 (90%)	4/39 (10%)	
NEC: SIP				
NEC (n = 47)		41/47 (87%)	6/47 (13%)	0.99
SIP (n = 18)		16/18 (89%)	2/18 (11%)	
Birth weight, g		830 (651–1085)	688 (628–710)	0.12
Gestation age, weeks		26 + 2 (24 + 5–28 + 2)	24 + 5 (24 + 1–26 + 5)	0.15
Age at first surgery, days		10 (6–21)	9 (6–16)	0.68
Apgar score	1 min	5 (3–6)	4 (3–5)	0.10
	10 min	7 (6–8)	5 (4–7)	0.04
Mechanical ventilation, weeks		5.0 (2.0–7.0)	6.0 (4.2–7.5)	0.59
Cerebral hemorrhage Grade	I–II	13 (23%)	1 (12%)	0.70
	III–IV	9 (16%)	2 (25%)	
Severe / moderate RDS		27 (48%)	6 (75%)	0.26
PDA, no therapy		31 (54%)	5 (63%)	0.78
PDA, medical therapy		13 (23%)	1 (12%)	
PDA, surgical therapy		13 (23%)	2 (25%)	
Other significant heart disease		9 (16%)	1 (12%)	0.75
PN lipid emulsion				
soy oil based (n = 24)		20 (35%)	4 (50%)	0.45
other (n = 41)		37 (65%)	4 (50%)	
Length of PN days		64 (36–150)	47 (26–69)	0.28
PN before surgery, days		1 (0–3)	1 (0–4)	0.90
EN started after surgery, days		15 (8–39)	22 (8–33)	0.68
Number of septicemias		1 (1–2)	2 (1–3)	0.64
Resection of small intestine %		20 (7.0–49)	14 (7.5–44)	0.85
Ileocecal valve				
intact (n = 43)		39 (68%)	4 (50%)	0.42
resected (n = 22)		18 (32%)	4 (50%)	
Reoperations (patients reoperated)		38 (67%)	5 (63%)	1.0
Reoperations (surgeries/patient)		1 (0–2)	1 (0–2)	0.91
Survival	3 months	56 (98%)	3 (38%)	p < 0.001
	2 years	52 (91%)	0 (0%)	p < 0.001

patients with IFAC occurred at a median 15 (8–36) days and without IFAC 8 (4–14) days after surgery.

3. Discussion

In the present study we analyzed the incidence, effect on overall mortality and risk factors of IFAC in prematures who underwent surgery for NEC or SIP over a 29-year period in the two largest Finnish NICUs. The main results of the present study were: 1) the overall incidence of IFAC was high (41%); 2) incidence of IFAC increased on the latter study period to 50%; 3) the strongest predisposing factors for IFAC were septicemias and reoperations; 4) mortality in patients with IFAC was 20%, and all patients with unresolved IFAC died.

The increase of the incidence of IFAC may be associated with the trend toward higher overall two-week survival at the latter study period. Higher two-week survival in turn has increased the amount of patients at risk of IFAC. According to a recent systematic review the incidence of pediatric cholestasis and liver disease associated with PN and IF has not changed from 1970s to 2000s [14].

In the series of Elfvin et al. the overall incidence of IFAC among 153 surgical NEC patients was 33%, and 49% of patients had IF lasting over 42 days and 16% over 90 days, respectively [15]. In the present study the overall incidence of IFAC was 41% with the percentage of patients with IF (*ie.* the percentage dependent on PN) at 90 days slightly higher (24%) than in the series of Elfvin et al. [15].

Mortality of IFAC did not change during the early and late study periods. In our series consisting of premature neonates, mortality

associated with IFAC was 20%. However, none of our patients with unresolved IFAC survived. IFAC, however, did not cause a statistically significant increase in overall mortality. In prematures with extremely low birth weight IFAC associated with intestinal disease has been reported to result in disastrous 77% mortality [16].

The most important risk factors for the development of IFAC were intestinal reoperations and septicemias. The indications of intestinal reoperations after surgery for NEC and SIP include recurrent NEC, anastomotic complications and intestinal obstruction. Reoperations delay the recovery of intestinal motility and administration of EN and may result to further reduction of small intestine and prolonged PN. Septicemias from PN catheter infections and intestinal bacterial translocation are very common among NEC patients with PN [17]. The association between septicemias and IFAC has been also reported by other studies [15,18]. In concordance with two previous studies by Duro D. et al. and Elfvin A. et al. [9,15], we found no association between gestational age and IFAC. In the present study, recovery from IF and resolution of IFAC benefited from the fact that small intestinal loss was less than 25% in more than 50% of patients and since majority of the patients were operated on at a low gestation age, compensatory growth of small intestine was to be expected. Thus majority of the survivors eventually had enough small intestine and were weaned PN. Contrary to the study by Duro et al. [9] we did not find preoperative PN a risk factor for IFAC. This is probably because the duration of preoperative PN in our patients was short compared with the study by Duro et al. We found that birth weight, relative loss of small intestine, loss of ileocecal valve, length of PN, start of EN and NEC remained significant factors in

univariate logistic regression analysis but not in multivariate analysis. In our series IFAC manifested median 18 days after surgery, that is, at a time when duration of PN was less than 50% of the median total duration of PN of 42 days. At the time of the manifestation of IFAC enteral nutrition had been started only in half of the affected patients. The early manifestation of IFAC may explain why neither the total length of PN, relative loss of small intestine nor the loss of ileocecal valve predicted IFAC in multivariable logistic regression analysis. IFAC in surgical NEC and SIP may have a multifactorial etiology that includes severity of the intestinal disease, long duration of PN and recurring septicemia, together with prematurity and immaturity of hepatic and intestinal function. Surgery itself is not a prerequisite for IFAC. Yan et al. [18] reported 5% incidence of cholestasis among 1074 nonsurgical premature neonates with prolonged (over 43 days) PN, and male sex and septicemia were found as the main risk factors for of cholestasis.

The adoption of alternative lipid emulsions has not been shown to change the incidence and outcome of IFAC [19]. With a retrospective design the present study was not well suited for comparison of lipid emulsions. We could not show that a change from soy-oil based to olive oil based PN emulsion had any effect on the development, duration or resolution of IFAC. In patients with PN more than 90 days we found that two-year survival in patients with soy oil based PN emulsion was lower than in patients with other PN emulsions. However, the significance of this finding is uncertain because other factors than PN may have affected mortality.

The weakness of the present study was its retrospective design. Under the study period from 1986 to 2014 neonatal care has undergone many changes such as ventilation techniques, medication and parenteral nutrition that unavoidably confound the final assessment of the results. Surgical techniques have not changed much except that during the latter study period drainage of the abdomen was introduced as an initial stabilizing measure. In the present series all patients who survived drainage eventually underwent a definite open surgical procedure. Moreover we could not include proper data of enteral nutrition (e.g. starting times, volumes), energy delivered by parenteral and enteral nutrition and the consistence of the nutrients in an individual patient in our statistical assessment. Total and conjugated bilirubin values were the most consistently serially measured blood tests among our patients whereas serial measurements of blood tests for liver function were unavailable in many patients and thus not presented.

The present study included in a national scale a substantial number of successive prematures who underwent surgery for NEC and SIP in two NICUs. The incidence of IFAC has increased but remains similar than reported incidence in contemporary literature. From our data we could not pinpoint the reason for the increased incidence of IFAC. The present study and other previous studies [16] support the fact that IFAC increases the risk of death. In patients who died with unresolved IFAC we could not assess the exact mechanism of death but we believe that unresolved IFAC with no signs of resolution is associated with significant metabolic derangement and impeded hepatic function and is a major contributor to death.

The present patient series is collected from a long period of time during which management of neonates has evolved significantly. However,

the incidence and surgical management of NEC and SIP in our series have not changed much from 1986 to 2014. It seems that the major hit in development of IFAC occurs early with the serious intestinal disease in a premature whereas after surgery the possibilities to prevent IFAC still remain limited. Comparing old patient material with new provides at least an insight in the changing risk of IFAC; with new neonatal treatment modalities, new PN emulsions, and the gathered knowledge of IF and IFAC, the incidence of IFAC has not decreased but increased. Even with its limitations, the present study provides an actual insight into the clinical course of NEC and SIP patients with IFAC.

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